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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,028	BUNSCHOTEN ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/05 and 12/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 were pending and subject to an Election/Restriction requirement. Claims 14-15 were withdrawn as being directed to a non-elected invention.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 1-13 and 16-20) and species recombinant FSH, ganirelix, recombinant LH, and urinary hCG in the reply filed on October 24, 2007 is acknowledged.

3. Claims 14-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 24, 2007.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-13 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated that, "To fulfill the written description requirement,

a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)("[T]"he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus an applicant complies with the written description requirement "by describing the invention, with all its claimed limitation, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co. 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated that, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 P.2d at 1171,25 USPQ2d 1601; in re Smylhe;480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily. chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is ':not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that flora generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus, see MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Goslelli, 872. F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any, combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a method of controlled ovarian hyperstimulation in a mammilian female, encompassing coadministration to the female of a substance having follicle stimulating hormone activity (FSH substance) in an amount effective to stimulate multiple follicular development; gonadotropin releasing hormone (GnRH) antagonist in an amount equivalent to a daily subcutaneous dose of at least 0.5 ganirelix to prevent a premature LH-surge, a substance having luteinising hormone activity (LH substance) in an amount effective to prevent or suppress symptoms of luteinising hormone (LH) deficiency resulting from the administration of the GnRH antagonist; followed by the administration of a meiosis and luteinisation inducing substance in an amount effective to stimulate resumption of meiosis and luteinisation, and wherein the LH substance is not obtained from the urine of human females.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is such that one understands COH/assisted reproductive technology to be an unpredictable method, highly dependent upon specific proportions and/or amounts of particular ingredients and thus, with a low success rate and risks associated with treatment. Some FSH, LH, hCG (ML) analogs and GNRH antagonists are known in the art, however the level of skill and knowledge in the art is low with regards to those compounds that are useful in COH. It is known in the art that GnRH is synonymous with LHRH. However, within the art, GnRH agonists are known which are structurally related to leuprorelin, however, the level of skill and knowledge in the art is low with regards to those compounds that are useful in COH.

(2) Partial structure:

The claims are silent with respect to any structure of FSH, LH, ML analogs. The claims recite two GnRH antagonists, i.e. ganirleix and cetrorelix. The specification provides one example of FSH substance, i.e. FSH (whether recombinant, synthetic or natural), one example of an LH substance, i.e. LH (whether recombinant, synthetic or natural), two GnRH antagonists, and three specific examples of ML substances, i.e. LH (whether recombinant, synthetic or natural), choriotropin gonadotropin (whether recombinant, synthetic or natural) and gonadotropin releasing hormone and GnRH agonists (no examples). The specification only discloses that the substances as used herein for example FSH substance encompasses substances that display a similar functionality as FSH, as well as substances which are capable of triggering the pituitary release of FSH, ML substances encompass substances that display a similar functionality as LH, as well as substances which are capable of triggering the pituitary release of LH, the term LH substance refers to substances that display a similar fuctionality as LH. Thus, the specification is essentially silent with regards to any compounds other than FSH, LH, choriotropin gonadotropin, and gonadotropin releasing hormone. The claims require co-administration to a mammalian female of any substance having follicle stimulating hormone activity in an amount effective to stimulate multiple follicular development; a gonadotropin releasing hormone (GnRH) antagonist in an amount equivalent to a daily subcutaneous dose of at least 0.5 mg ganirelix to prevent a premature LH-surge; a substance having luteinising hormone activity (LH substance) in an amount effective to prevent or suppress symptoms of luteinising hormone (LH) deficiency resulting from administration the administration of the GnRH antagonist; followed by the administration of a meiosis and luteinisation inducing substance (ML

substance) in an amount effective to stimulate resumption of meiosis and luteinisation, and wherein the LH substance is not obtained from the urine of human females.

(3) Physical and/or chemical properties

The claims are silent to physical and/or chemical properties. The only activities alluded to in the specification are for FSH causing follicle maturation and luteinising hormone, which causes ovulation. The specification also discloses that GnRH antagonists were introduced to prevent premature LH surges and to avoid the problems related to the use of GnRH agonists, i.e. ganirelix prevents premature LH rises to occur and at the same time maintains sufficient LH to support follicular maturation and estrogen biosynthesis and centrorelix selectively suppresses the secretion of LH. However, these activities are not extrapolated to anything other than ganirelix and centrorelix, respectively.

(4) Functional Characteristics

The specification only discloses that the substances as used herein for example FSH substance encompasses substances that display a similar functionality as FSH, as well as substances which are capable of triggering the pituitary release of FSH, ML substances encompass substances that display a similar functionality as LH, as well as substances which are capable of triggering the pituitary release of LH, the term LH substance refers to substances that display a similar fuctionality as LH. However, the specific activities encompassed are not disclosed. Additionally, functional characteritics of the GnRH agonists or antagonists are not set forth except as they pertain to an FSH substance, an LH substance or an ML substance.

(5) Method of making/using the claimed invention

While the steps involved in COH, ART, IUI and IVF are generally known using FSH alone or in combination with LH, ganirelix or centrorelix and CG, and general peptide synthesis is well known in the, the specification does not provide sufficient guidance as to how one would make the genuses of FSH substance, LH substances, GnRH antagonists and ML substances that would be used in COH, ART, IUI and IVF.

As state supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 1-13, and 16-20 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any FSH, LH and ML substances and GnRH antagonists. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the specification. Moreover, the specification lack sufficient variety of species to reflect these vaiances in the genuses. While having written description of the particular GnRH antagonists of claim 9 and compounds identified in the specification and/or examples, the specification does not provide sufficient desciptive support for the myriad of compounds embraced by the claims, i.e. the "substances" and GnRH antagonists.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736, F.2d 1516, 1521,222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed

that the specification fails to provide adequate written description for the genuses of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-13 and 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants claim a method of using substances by their activity. However, the activity is vague and indefinite one does not know what activities are encompassed by substances having follicle stimulating hormone activity, substances having luteinising hormone activity because Applicants have defined the activity by the name of specific hormones not by what they do, i.e. receptor binding, follicle maturation, ovulation. One does not know what specific activity would be utilized to make them a FSH substance or a LH substance.

8. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are:recombinant LH per kg of body weight. The claim originally included the language recombinant LH per kg of body weight. Applicant deleted this language. The specification on page 6 incorporates this language when speaking of the ranges. It is believed that this was an inadvertent deletion and appropriate correction is required. The claim has been interpreted as having this limitation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 6-13, 16-17, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grondahl, et al. (US 6,585,982) in view of Matthieu, et al. (US 2003/0092628) and further in view of Hideyuki Ikenaga, The Clinical Significance of the Ratio in FSH/LH of Human Menopausal Gonadotropins in a Programmed Stimulation Regimen for IVF-ET, Acta Obst. Gynaec. JPN, 1995, Vol. 47, No. 11, pp. 1223-1229 and Christina Bergh, Recombinant follicle stimulating hormone, Hum. Reprod., 1999, Vol. 14, No. 6, pp. 1418-1419.

Grondahl discloses that in vitro fertilization (IVF) [includes controlled ovarian hyperstimulation] of human oocytes has become commonly used for the treatment of female and male subfertility with the standard IVF treatment including a long phase of hormone stimulation of the female patient, e.g. 30 days, which is initiated by suppressing the patient's own follicle stimulating hormone (FSH) and luteinising hormone (LH) by gonadotropin releasing hormone (GnRH), and this is followed by injections of exogenous gonadotropins, e.g. FSH and/or LH in order to ensure development of multiple preovulatory follicles and aspiration of multiple in vivo matured oocytes immediately before ovulation and further, aspirated oocyte is subsequently fertilized in vitro and cultured, typically for 3 days before transferal back into the uterus at the 4-8 cell stage. Col. 1, lines 25-38. Grondal refers to the female cycle, as a way of performing IVF is as follows:

"Around day 21 in one cycle to around day 15 in the following cycle: The eggs are stimulated by treating the woman with GnRH, e.g. Synarel (400-600 micrograms per day).

Around days 6-16 in the second cycle: The eggs are stimulated by treating the woman with FSH, e.g. Gonal-F [FSH preparation], Puregon [recombinant FSH], or Humegon (hMG – a combination of FSH and LH] (150-400 IU per day). [a substance having follicle stimulating hormone activity in an amount effective to stimulate multiple follicular development and includes a substance having luteinising hormone activity and it is in an amount effective to prevent or suppress symptoms of LH deficiency, which would result from administration of a gonadotropin releasing hormone antagonist as it is within the ranges disclosed by Applicants for this effect, i.e. between 1 and 40 IU recombinant LH per kg of body weight][1]

Around days 15-16 in the second cycle: The eggs are stimulated by treating the woman with hCG, e.g. Pregnyl or Profasi (2000-5000 IU per day)[followed by administration of a meiosis and luteinisation inducing substance in an amount effective to stimulate resupmtion of meiosis and luteinisation].

Around day 18 in the second cycle: The eggs are retrieved from the woman [harvesting one or more ova from mature ovarian follicles].

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[1] Women typically weigh between 42 to 120 kg. See, e.g. Womens average weight chart and percentile distribution - A weight chart for women of "White" race/ethnicity, showing – average weight changes with age, 2000, pp. 1-2, http://www.halls.md/chart/women-weight-w.htm; Women's Weight Chart for women of "Black" race/ethnicity, showing weight changes with age, 2000, pp. 1-2, http://www.halls.md/on/women-weight-b.htm; Women's Weight Chart for women of "Mexican-American" race/ethnicity, showing weight changes with age, 2000, pp. 1-2, http://www.halls.md/on/women-weight-h.htm; Women's Weight Chart for women of "Other" race/ethnicity, showing weight changes with age, 2000, pp. 1-2, http://www.halls.md/on/women-weight-o.htm. Thus, the range of administration would be 42 to 4800 IU of recombinant LH.or 84 to 1800 IU of recombinant LH and would be effective to maintain the females blood serum concentration of LH substances at a level equivalent to more than 1 I.U. per LH.

Around day 18-19 in the second cycle the eggs are maturated with a MAS compound in order to stimulate meiosis. In this additional maturation stem, step, the concentration of MAS compound may be in the range about 0.1-100 micromol per liter ...

Around days 19-21 in the second cycle: The eggs are fertilized in vitro. ...

Around day 21 in the second cycle: One or more embryos are transferred to the woman's uterus. Col. 2, lines 20-65.

However, Grondal does not disclose that a gonadotropin releasing hormone antagonist is administered or that the LH can be recombinant LH. The examiner notes that the other limitations of claim 1 and 13 are met, as are the limitations of claims 2, 3, 6, 7, 8, 16 and 20 are met by the above disclosure. Because the amounts used and periods of time are encompassed by the above disclosure the compounds would have the same effects. The examiner also notes that the LH substance would be administered in an amount effective to maintain the females blood serum concentration of LH substances at a level equivalent to more than 1 I.U. LH/liter because the amount and the duration are within the specified ranges of dosing and this would implicitly cause the blood serum concentration to be more than 1.2 I.U. LH/liter.

Matthieu discloses GnRH antagonists and ganirelix, in particular, as compared to GnRH agonists,[2] in controlled ovarian hyperstimulation (COH) as well as to prevent premature LH surge, i.e. by GnRH receptor competition provide an immediate inhibition of gonadotropin secretion, especially of LH and thus, during COH by FSH, GnRH antagonist treatment is only required during the few days when there is an increased risk for a premature LH surge, noting

[2] Noting the disadvantages with GnRH agonists, i.e. the initial flare-up and the rather long period until pituitary suppression becomes effective – usually patients undergoing COH start only treatment with (recombinant) FSH after 2 to 3 weeks pretreatment with GnRH agonists. Col. 1 - [0005].

that the GnRH antagonist dosage range is critical: too low a GnRH antagonist dosage leading to premature LH rises, while too high a GnRH antagonist dosage hampered follicular maturation with a dosing for human therapy a daily range is suggested for administration of the active ingredient between 0.001 and 5 mg/kg, preferably between 0.01 and 1 mg/kg. Col. 1 – [0001]-[0007]. The examiner notes that the average female weight is about 60 kg and this would definitely be at least 0.5 mg using the preferred range and heavier women would use the range of 0.8- greater than 4.0 mg ganirelix. Matthiem additionally discloses that the preparation is administered parentally[3], together with FSH during the days of ovarian stimulation when a premature LH rise may easily occur, e.g. from day 5 of FSH administration onwards and administration is usually stopped when sufficient follicles have matured and exogenous hCG/LH is given for induction of ovulation, the amounts usually are 5000-10,000 IU, however, the exact regimen might depend on the individual response and is finally to be decided by the clinician who treats the subject, however, FSH treatment starts at menses day 1, 2, or 3and ovarian stimulation with FSH, preferable recombinant FSH, alone may be continued up to 5 days in an amount of e.g. 150-225 IU with treatment with GnRH antagonist, ganirelix, may be started at the first day of FSH but preferably such treatment starts at FSH treatment day 4 or 5 and may last 2-14 days, i.e. up to the moment whereupon the patient is treated with exogenous LH/hCG for ovulation induction. Cols. 1-2, [0009]-[0019], Examples, and claims 1-2 and 6-7. It would have been obvious to one of ordinary skill in the art at the time of the invention to have added the step of a gonadotropin releasing hormone antagonists, i.e. ganirelix, to the method of Grondal because the gonadotropin releasing antagonists prevent premature LH surge, thus allowing for

[3] Preferably it is administered subcutaneously, particularly in the form of liquid solutions or suspension with glacial

maturation of more oocytes and the antagonists do not have the disadvantages associated with GnRH antagonists.

Ikenaga discloses a comparison of hMG preparation with different FSH/LH ratios to determine their clinical effectiveness in a programmed stimulation regimen for IVF-ET, where eighty-four IVF-ET candidates at Toho University Hospital received injections of an hMG preparation containing a 3:1 ratio of FSH/LH: Group A, 36 patients received hMG at an FSH/LH 1:1 ratio: Group B, and 20 patients received pure FSH: Group C - all received injections of 3000IU hMG daily for 7 days according to our COH protocol. Ikenage additionally discloses the results of the comparison was determined by analysis of serum levels of E2, number of mature follicles, number of retrieved oocytes, fertilization rate, cleavage rate, number of transferred embryos ad pregnancy rate. Ikenage further disclosed the results were as follows:

1. The serum E2 level was higher in Group A than in Croup C with significant differences.
2. The oocyte retrieval rate was significantly higher in Group A.
3. The rate of equally cleaved eggs was significantly higher in Group A.
4. The pregnancy rate was significantly higher in Group A.

Ikenaga concludes that an hMG preparation containing a 3:1 FSH/LH ratio was most suitable in our COH protocol. It would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized a 3:1 ratio of FSH/LH in the combined method of Grondal and Matthiem to achieve a higher serum E2 level, higher oocyte retrieval rate, higher rate of equally cleaved eggs and a significantly higher pregnancy rate. Noting that the LH disclosed would be divided by 3.

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acetic acid, mannitol, and water adjusted to pH5 with sodium hydroxide and/or hydrochloric acid. Col. 2, [0019].

Bergh discloses that recombinant gonadotrophin bear clear advantages in comparison with the older urinary preparations, i.e. guarantees high availability of a biochemically pure FSH [also holds true for LH] preparation free from urinary protein contaminants, which high purity and low immunogenicity allows s.c. administration. Bergh also discloses that recombinant FSH [also hold true for LH] advantageously provides constant availability batch to batch. Bergh concludes that the newly developed recombinant gonadotrophins have clear advantages, particularly in purity, availability and batch consistency. It would have been obvious to one of ordinary skill in the art to make a recombinant FSH:LH in a three to one ratio in the combined method of Grondal and Matthiem to achieve better purity, availability and batch consistency of the FSH:LH and thus increase the serum E2 levels, increase the oocyte retrieval rate, increase the rate of equally cleaved eggs, and increase pregnancy rates. One would have had a reasonable expectation for success in administering a recombinant FSH:LH ratio of 3:1 in the combined method of Grondal and Matthiem, as these are the same compounds merely made recombinantly and with the dosage changed to 3:1, techniques widely practiced in the pharmaceutical arts, and because Ikenga discloses the specific advantages to such a ratio, while Bergh discloses specific advantages of making them recombinantly.

9. Claims 1-13, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grondahl, et al. (US 6,585,982) in view of Matthieu, et al. (US 2003/0092628) and further in view of Hideyuki Ikenaga, The Clinical Significance of the Ratio in FSH/LH of Human Menopausal Gonadotropins in a Programmed Stimulation Regimen for IVF-ET, Acta Obst. Gynaec. JPN, 1995, Vol. 47, No. 11, pp. 1223-1229 and Christina Bergh, Recombinant follicle stimulating hormone, Hum. Reprod., 1999, Vol. 14, No. 6, pp. 1418-1419 and further in view of

Scott, et al., Correlation of Follicular Diameter with Oocyte recovery and Maturity at the Time of Transvaginal Follicular AspirationJournal of in Vitro Fertilization and Embryo Transfer, 1989, Vol. 6, No. 2, pp. 73-75.

Grondal, Matthieu, and Ikenaga disclose as set forth infra. However none of them disclose that the GnRH antagonist is administered when the largest developing ovarian follicle has reached an average diameter of 14 mm or 12 mm or 10 mm. Scott discloses that the probability of retrieving a metaphase I or II oocytes was significantly lower in follicles <11 mm and only somewhat higher in 12-14-mm follicles and equally high among the other groups and he concluded that follicles >15 mm provide the highest probability of retrieving mature oocytes and that metaphase I and metaphase II oocytes significantly outperform prophase I oocytes, even after controlling for fertilization. Pg. 73. Scott concludes that information regarding the probability of recovering oocytes in different maturational states has direct clinical relevance. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered the ganirelix when the oocytes were 10, 12 or 14 mm in the method of Grondal/Matthieu/Ikenga because you would want to optimize the number of oocytes that become greater than 15 mm by preventing a premature LH surge in order to obtain more metaphase I and metaphase II oocytes to get the better performance in your COH/IVF/ART.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer I. Harle
Examiner
Art Unit 1654

December 26, 2007